

Incidence and prognostic factors of patients with synchronous liver metastases upon initial diagnosis of breast cancer: a population-based study

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Background: The purpose of this study was to analyze the incidence and prognostic factors of patients with breast cancer liver metastases (BCLM) at initial diagnosis.

Methods: We utilized the Surveillance, Epidemiology, and End Results database to extract data on patients with primary invasive breast cancer from 2010 to 2014. Multivariate logistic regression was conducted to determine factors associated with the presence of liver metastases upon initial diagnosis of breast cancer. Univariate and multivariate Cox regression analyses were performed to identify the prognostic factors in these patients.

Results: In total, 3,276 patients with liver metastases were identified upon initial diagnosis of breast cancer. Patients with hormone receptor-negative (HR-), human epidermal growth factor receptor 2-positive (HER2+) breast cancer had the highest incidence (4.6% among the entire population, 46.5% among the metastatic subgroup). Age, gender, race, pathological grade, extrahepatic metastases, tumor subtype, and marital status were identified as factors associated with the presence of liver metastases upon initial diagnosis of breast cancer. The median overall survival among the entire population with BCLM was 20.0 months. Patients with HR+/HER2+ breast cancer had the longest median survival of 36.0 months. The survival analyses indicated that older age, higher pathological grade, extrahepatic metastases, triple-negative subtype, unmarried status, and uninsured status were independent prognostic factors for a poorer prognosis.

Conclusion: The study provides insight into the incidence and prognostic factors for patients with BCLM at initial diagnosis, which is important clinical information for risk evaluation and prognostic assessment.

Keywords: breast cancer, liver metastases, incidence, prognostic factors, breast cancer subtype

Introduction

According to the latest overview of cancer statistics, breast cancer is the most frequently diagnosed cancer and is the leading cause of cancer death among women worldwide.¹ The survival of breast cancer patients is strongly stage dependent. Specifically, the 5-year relative survival of patients with localized tumors can be as high as 98.6%, compared with 83.8% for patients with regional tumors and 23.3% for patients with distant metastases.² In addition, ~6% of patients present with metastatic disease at initial diagnosis, while ~30% of patients first diagnosed with early-stage disease eventually develop metastatic disease.^{3,4}

It is widely recognized that breast cancer is a heterogeneous disease and can be categorized into several distinct molecular subtypes based on the presence of estrogen

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receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2).^{5,6} Recent studies imply that the distinct subtypes have different prognoses and anticancer therapy responses.^{7,8} Additionally, there is growing evidence indicating that different molecular subtypes have their own specific sites of distant metastases. Hormone receptor-positive (HR+) breast cancer preferentially metastasizes to bone, while the HER2-positive (HER2+) subtype and triple-negative breast cancer tend to metastasize to visceral organs such as the brain, liver, and lung.^{9–13}

Notably, relative to the bone, lung, and brain, liver is one of the most common breast cancer metastatic sites, with clinical and autopsy incidence of 40%–50% and 50%–62%, respectively, among all metastatic breast cancers.^{14–17} Liver metastases may present asymptotically or with abdominal discomfort, ascites, jaundice, abnormal function tests, hepatomegaly, or abdominal pain.^{18–20} Patients with breast cancer liver metastases (BCLM) can experience refractory complications including sudden hepatic failure, refractory ascites, esophageal varices, portal vein thrombosis, and nutritional compromise.²⁰ Earlier studies reported that the involvement of visceral metastases, especially liver metastases, is a sign of poor survival.^{21,22} The median survival time of patients with BCLM is only 4–8 months without treatment.²³ Research on metastasis mechanisms and organotropism may assist in improving the outcome of patients with BCLM. Furthermore, circulating tumor cells and Flammer syndrome had been studied to select and stratify potentially predisposed to liver metastases among patients with breast cancer.²⁴

In the present study, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to study patients with BCLM at initial diagnosis stratified by breast cancer subtype. The goals of this study were: 1) to evaluate the clinicopathological characteristics of patients with BCLM, 2) to calculate the relative incidence of patients with BCLM, and 3) to determine the factors associated with the presence of liver metastases and the survival of patients with BCLM at initial diagnosis.

Methods

Database

SEER database consisting of 18 population-based cancer registries includes information on cancer incidence, patient characteristics, primary tumor site, tumor morphology, treatment, and survival of ~30% of the US population. The datasets of the current study are available from SEER Program (<https://seer.cancer.gov/>) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana

Cases, Nov 2016 Sub (1973–2014 varying), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2017, based on the November 2016 submission.

Study population

Because SEER began collecting sites of metastasis at initial diagnosis in 2010, we set the starting point of our study as 2010. We extracted 228,300 patients 18 years or older who were diagnosed with primary and histologically validated malignant breast cancer as the only primary malignancy between 2010 and 2014. Patients with carcinoma in situ and an unknown state of liver metastases were excluded from this cohort, leaving 224,449 patients in the final cohort for incidence analysis. Of these, 3,281 patients had liver metastases when first diagnosed with breast cancer. We subsequently excluded patients who were diagnosed by autopsy or death certificate, as well as patients who had an unknown follow-up or whose survival record presented with 0 months for the survival analysis, leaving 213,945 patients, among whom there were 2,804 patients diagnosed with liver metastases.

Ethics statement

Our study was approved by an independent ethical committee/institutional review board at Fudan University Shanghai Cancer Center (Shanghai Cancer Center Ethical Committee). The data released by the SEER database do not require informed patient consent for cancer is a reportable disease in every state in the USA.

Statistical analysis

Study variables, including age at diagnosis, year of diagnosis, sex, race, histology, pathological grade, type of breast cancer surgery, site of metastases, marital status, and insurance status, were enrolled into the descriptive statistics to evaluate the patient characteristics stratified by breast cancer subtype, which were classified into HR-positive/HER2-negative (HR+/HER2-), HR-positive/HER2-positive (HR+/HER2+), HR-negative/HER2-positive (HR-/HER2+), and triple-negative. In the SEER database, pathological grades were categorized into I (well differentiated), II (moderately differentiated), III (poorly differentiated), and IV (undifferentiated or anaplastic). Chi-square or Fisher's exact tests were used as appropriate.

Incidence was defined as the number of patients with liver metastases divided by the total number of patients with breast cancer. We calculated the incidence of patients with liver metastases among the entire cohort and metastatic subgroup stratified by breast cancer subtype.

We used multivariable logistic regression to determine whether age at diagnosis, sex, race, marital status, and insurance status were associated with the presence of liver metastases at diagnosis; other variables, namely, histology, pathological grade, breast cancer subtype, and number of extrahepatic metastatic sites, including the lung, bone, and brain, were also enrolled into this model. ORs and 95% CIs from the logistic regression model are reported.

Overall survival (OS) was defined as the date of diagnosis to the date of death regardless of whether the death was caused by breast cancer, and breast cancer-specific survival (BCSS) was calculated from the date of diagnosis to the date of death due to breast cancer. We utilized the Kaplan–Meier method to obtain survival estimates and generate survival curves within subsets and analyzed the differences using log-rank tests. Univariable and multivariable Cox proportional hazards models were constructed to assess the association of the variables as described in the logistic regression model with increased all-cause mortality and breast cancer-specific mortality. We calculated hazard ratios and 95% CIs in the Cox regression model.

All the statistical analyses were performed using SPSS statistical software version 22.0 package (IBM Corporation, Armonk, NY, USA). All reported *P*-values were two-sided, and a *P*-value of 0.05 or less was considered as statistically significant.

Results

Patient characteristics

A total of 224,449 patients were diagnosed with breast cancer from 2010 to 2014 in the USA and were enrolled in the incidence analysis. Among the entire population, 3,276 patients had liver metastases at the initial diagnosis of breast cancer, and Table 1 summarizes their clinicopathological characteristics according to breast cancer subtype. Patients with HR+/HER2–, HR+/HER2+, HR–/HER2+, triple-negative, and unknown subtype, respectively, accounted for 38.9%, 20.5%, 14%, 13.2%, and 13.4%, and only 851 patients had metastatic disease confined to the liver (26.0%). Compared with other patients, HR+/HER2– breast cancer patients with liver metastases were older ($P<0.001$), had a higher rate of invasive lobular carcinoma pathology ($P<0.001$), had a lower pathological grade ($P<0.001$), and had a higher rate of no surgery for breast cancer ($P<0.001$). In contrast, triple-negative breast cancer patients with liver metastases had a higher rate of pathological grade III/IV ($P<0.001$), had a higher rate of breast cancer surgery ($P<0.001$), and presented with more extrahepatic metastatic sites ($P<0.001$).

Incidence

In the total of 224,449 patients, 11,997 patients were diagnosed with metastatic disease. Table 2 displays the result of incidence of liver metastases stratified by breast cancer subtype among the entire population and the metastatic subgroup. A total of 3,276 patients diagnosed with liver metastases accounted for 1.5% of the entire population and 27.3% of the metastatic subgroup. Patients with HR–/HER2+ (4.6% of the entire population, 46.5% of the metastatic subgroup) and patients with HR+/HER2+ (2.9% of the entire population, 37.5% of the metastatic subgroup) had the highest incidence of liver metastases, while patients with HR+/HER2– (0.8% of the entire population, 20.6% of the metastatic subgroup) had the lowest incidence.

The multivariable logistic regression was performed among the entire population and the metastatic subgroup (Table 3). Among the entire population, female sex (vs male sex, $P=0.001$); black race (vs white race, $P=0.025$); pathological grade II (vs grade I, $P<0.001$) and grade III/IV (vs grade I, $P<0.001$); metastatic diseases to one extrahepatic site (vs 0 extrahepatic site, $P<0.001$), two extrahepatic sites (vs 0 extrahepatic site, $P<0.001$), and three extrahepatic sites (vs 0 extrahepatic site, $P<0.001$); and HR+/HER2+ (vs HR+/HER2– subtype, $P<0.001$), HR–/HER2+ (vs HR+/HER2– subtype, $P<0.001$), and triple-negative subtypes (vs HR+/HER2– subtype, $P<0.001$) were significantly associated with an increased risk of having liver metastases at diagnosis. Age 41–60 years (vs age 18–40 years, $P=0.001$), age 61–80 years (vs age 18–40 years, $P<0.001$), age >80 years (vs age 18–40 years, $P<0.001$), and married status (vs unmarried, $P=0.005$) were significantly associated with a lower risk of having liver metastases at diagnosis. Neither histology nor insurance status was associated with the risk of having liver metastases at initial diagnosis of breast cancer in this model. Among the metastatic subgroup, age, sex, histology, pathological grade, extrahepatic metastatic sites, and tumor subtype were associated with the presence of liver metastases at diagnosis of breast cancer ($P<0.05$).

Survival analysis

A total of 2,804 patients with complete follow-up time were included in the survival analysis. The median OS among patients with BCLM was 20.0 months (Figure 1A). OS estimates stratified by breast cancer subtype is displayed in Figure 1B (log-rank test, $P<0.001$). Patients with HR+/HER2+ subtype had the longest median survival (36.0 months), while patients with triple-negative subtype had the shortest median survival (9.0 months). Significant difference was shown when

Table 1 Clinicopathological characteristics of patients with liver metastases according to breast cancer subtype

Patient characteristics	Breast cancer subtype										Total		P-value
	HR+/HER2-		HR+/HER2+		HR-/HER2		Triple-negative		Unknown				
	N	%	N	%	N	%	N	%	N	%	N	%	
All patients	1,257	38.9	670	20.5	460	14	432	13.2	438	13.4	3,276	100	
Age at diagnosis, years													
18–40	124	9.7	99	14.8	64	13.9	45	10.4	17	3.9	349	10.7	<0.001*
41–60	571	44.7	332	49.6	231	50.2	208	48.1	195	44.5	1,537	46.9	
61–80	478	37.5	202	30.1	142	30.9	153	35.4	173	39.5	1,148	35	
>80	103	8.1	37	5.5	23	5	26	6	53	12.1	242	7.4	
Year of diagnosis													
2010	210	16.5	102	15.2	68	14.8	75	17.4	111	25.3	566	17.3	<0.001*
2011	256	20.1	119	17.8	89	19.3	84	19.4	100	22.8	648	19.8	
2012	251	19.7	158	23.6	83	18	78	18.1	69	15.8	639	19.5	
2013	295	23.1	126	18.8	99	21.5	104	24.1	85	19.4	709	21.6	
2014	264	20.7	165	24.6	121	26.3	91	21.1	73	16.7	714	21.8	
Sex													
Male	5	0.4	6	0.9	1	0.2	1	0.2	7	1.6	20	0.6	0.025*
Female	1,271	99.6	664	99.1	459	99.8	431	99.8	431	98.4	3,256	99.4	
Race													
White	950	74.5	495	73.9	336	73	300	69.4	323	73.7	2,404	73.4	0.052
Black	220	17.2	119	17.8	78	17	106	24.5	81	18.5	604	18.4	
Asian/Pacific Islander	89	7	50	7.5	42	9.1	25	5.8	32	7.3	238	7.3	
American India/Alaska	10	0.8	6	0.9	2	0.4	1	0.2	2	0.5	21	0.6	
Unknown	7	0.5	0	0	2	0.4	0	0	0	0	9	0.3	
Histology													
IDC	881	69	551	82.2	373	81.1	347	80.3	199	45.4	2,351	71.8	<0.001*
ILC	148	11.6	22	3.3	2	0.4	11	2.5	25	5.7	208	6.3	
Others ^a	247	19.4	97	14.5	85	18.5	74	17.1	214	48.9	717	21.9	
Pathological grade													
I	87	6.8	12	1.8	1	0.2	3	0.7	11	2.5	114	3.5	<0.001*
II	461	36.1	207	30.9	114	24.8	66	15.3	70	16	918	28	
III/IV	462	36.2	356	53.1	272	59.1	304	70.4	118	26.9	1,512	46.2	
Unknown	266	20.8	95	14.2	73	15.9	59	13.7	239	54.6	732	22.3	
Surgery													
No surgery	1,015	79.5	491	73.3	337	73.3	286	66.2	388	88.6	2,517	76.8	<0.001*
BCS	81	6.3	52	7.8	33	7.2	51	11.8	12	2.7	229	7	
Mastectomy	174	13.6	122	18.2	84	18.3	92	21.3	30	6.8	502	15.3	
Unknown	6	0.5	5	0.7	6	1.3	3	0.7	8	1.8	28	0.9	
Number of extrahepatic metastatic sites to lung, bone, and brain													
0	282	22.1	191	28.5	159	34.6	129	29.9	90	20.5	851	26	<0.001*
1	536	42	276	41.2	161	35	179	41.4	169	38.6	1,321	40.3	
2	319	25	146	21.8	82	17.8	77	17.8	104	23.7	728	22.2	
All 3	56	4.4	20	3	25	5.4	27	6.3	17	3.9	145	4.4	
Unknown	83	6.5	37	5.5	33	7.2	20	4.6	58	13.2	231	7.1	
Marital status													
Unmarried ^b	651	51	331	49.4	226	49.1	223	51.6	233	53.2	1,664	50.8	0.366
Married	540	42.3	295	44	211	45.9	183	42.4	168	38.4	1,397	42.6	
Unknown	85	6.7	44	6.6	23	5	26	6	37	8.4	215	6.6	
Insurance status													
Uninsured	56	4.4	40	6	18	3.9	28	6.5	27	6.2	169	5.2	0.046*
Insured	1,196	93.7	616	91.9	435	94.6	393	91	393	89.7	3,033	92.6	
Unknown	24	1.9	14	2.1	7	1.5	11	2.5	18	4.1	74	2.3	

Notes: ^aIncluding other histology of invasive breast cancer except IDC and ILC; ^bincluding divorced, separated, single (never married), and widowed; + denotes positive; – denotes negative; *denotes a statistically significant P-value.

Abbreviations: BCS, breast conserving surgery; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma.

Table 2 Incidence and median OS of patients with liver metastases at initial diagnosis of breast cancer stratified by breast cancer subtype

Breast cancer subtype	Number of patients			Incidence of liver metastases, %		Survival among patients with liver metastases, medium (IQR), months
	With breast cancer	With metastatic disease	With liver metastases	Among entire population	Among metastatic subgroup	
HR+/HER2-	151,039	6,202	1,276	0.8	20.6	21.0 (7.0–43.0)
HR+/HER2+	22,834	1,786	670	2.9	37.5	36.0 (14.0–NR)
HR- /HER2+	9,964	989	460	4.6	46.5	29.0 (9.0–48.0)
Triple-negative	24,463	1,524	432	1.8	28.4	9.0 (4.0–17.0)
Unknown	16,149	1,496	438	2.7	29.3	13.0 (3.0–29.0)
All subtypes	224,449	11,997	3,276	1.5	27.3	20.0 (6.0–45.0)

Notes: + denotes positive; – denotes negative.

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IQR, interquartile range; NR, not reached; OS, overall survival.

stratified by the extent of extrahepatic metastatic disease (Figure 1C; log-rank test, $P<0.001$). Patients with more number of extrahepatic metastatic sites had worse prognosis.

The impact of the presence of extrahepatic metastases on OS among the patients with BCLM is graphically displayed in Figure 2. Patients with liver and other metastases had significantly shorter survival as compared with patients with liver metastases only (Figure 2A; log-rank test, $P<0.001$). Individually, patients with bone metastases had significantly shorter survival than those without bone metastases (Figure 2B; log-rank test, $P<0.001$). Similar findings were seen for patients with lung metastases vs no lung metastases (Figure 2C; log-rank test, $P<0.001$) and patients with brain metastases vs no brain metastases (Figure 2D; log-rank test, $P<0.001$).

Among the entire population, there were 8,442 patients with extrahepatic metastatic disease. The impact of the presence of liver metastases on the median survival of these patients stratified by the extent of extrahepatic metastatic sites in different breast cancer subtypes is provided in Table 4. Generally, patients with no baseline liver metastases had a longer median survival than patients with liver metastases. Specifically, there were significant differences in patients with bone and liver metastases vs those with bone metastases only (log-rank test, $P<0.001$) and patients with lung and liver metastases vs those with lung metastases only (log-rank test, $P<0.001$). However, there was no significant difference in OS between patients with brain and liver metastases vs those with brain metastases only (log-rank test, $P=0.261$). Furthermore, the abovementioned findings were observed in different breast cancer subtypes except for the HR-/HER2+ subtype.

Univariate and multivariate Cox proportional hazards models were conducted to assess the prognostic factors of patients with BCLM (Table 5). In the univariate Cox models, age at diagnosis, type of breast cancer surgery treatment, number of extrahepatic metastatic sites, breast cancer subtype, marital status, and insurance status were significantly associated with OS and BCSS ($P<0.05$). The multivariate Cox analysis identified that age at diagnosis, pathological grade, type of breast cancer surgery treatment, number of extrahepatic metastatic sites, breast cancer subtype, marital status, and insurance status were independent prognostic factors for OS and BCSS ($P<0.05$).

Discussion

Distant metastasis of breast cancer is a main public health concern affecting women worldwide.¹ Liver metastases is the third most common distant metastatic site for breast cancer.²⁵ In addition, BCLM remains an essential clinical problem due to its poor prognosis and limited response to systemic treatment. Golubnitschaja and Sridhar summarized the information about risk assessment and prognostic factors of liver metastases in colorectal, breast, and prostate cancers and recommended the analysis of molecular and pathology specific patterns in blood samples of individual patient, which could provide help for the diagnosis and treatment of liver metastases.²⁶ Besides, the multi-omics approach like proteomics, metabolomics, and bioinformatic analysis in the blood samples could be of great clinical utility for disease prevention, patients stratification, and disease treatment.^{27,28} There are several studies evaluating the dis-

Table 3 Multivariate logistic regression for the presence of liver metastases at initial diagnosis of breast cancer

Variables	Among entire population		Among metastatic subgroup	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age at diagnose, years				
18–40	1 (reference)		1 (reference)	
41–60	0.798 (0.696–0.916)	0.001*	0.842 (0.723–0.980)	0.026*
61–80	0.596 (0.517–0.687)	<0.001*	0.617 (0.528–0.721)	<0.001*
>80	0.556 (0.458–0.675)	<0.001*	0.554 (0.451–0.682)	<0.001*
Sex				
Male	1 (reference)		1 (reference)	
Female	2.250 (1.381–3.666)	0.001*	2.526 (1.546–4.128)	<0.001*
Race				
White	1 (reference)		1 (reference)	
Black	1.131 (1.015–1.259)	0.025*	1.018 (0.909–1.141)	0.754
Asian/Pacific Islander	0.891 (0.764–1.038)	0.137	0.915 (0.774–1.082)	0.299
American India/Alaska	0.927 (0.566–1.518)	0.763	0.993 (0.579–1.702)	0.978
Unknown	0.484 (0.247–0.949)	0.035*	0.485 (0.229–1.025)	0.058
Histology				
IDC	1 (reference)		1 (reference)	
ILC	0.958 (0.815–1.127)	0.608	0.780 (0.658–0.924)	0.004*
Others ^a	1.008 (0.907–1.121)	0.877	0.886 (0.791–0.992)	0.035*
Pathological grade				
I	1 (reference)		1 (reference)	
II	2.013 (1.641–2.468)	<0.001*	1.243 (0.993–1.555)	0.057
III/IV	2.757 (2.245–3.385)	<0.001*	1.431 (1.144–1.792)	0.002*
Unknown	3.344 (2.692–4.153)	<0.001*	1.465 (1.162–1.847)	0.001*
Number of extrahepatic metastatic sites to lung, bone, and brain				
0	1 (reference)		1 (reference)	
1	47.726 (43.418–52.462)	<0.001*	0.418 (0.375–0.466)	<0.001*
2	107.212 (95.302–120.611)	<0.001*	0.920 (0.809–1.046)	0.203
All 3	220.416 (169.800–286.122)	<0.001*	1.936 (1.490–2.516)	<0.001*
Unknown	152.389 (125.913–184.432)	<0.001*	1.966 (1.593–2.426)	<0.001*
Breast cancer subtype				
HR [±] /HER2–	1 (reference)		1 (reference)	
HR [±] /HER2+	2.353 (2.106–2.630)	<0.001*	2.066 (1.833–2.330)	<0.001*
HR–/HER2	3.746 (3.271–4.290)	<0.001*	2.698 (2.327–3.129)	<0.001*
Triple-negative	1.483 (1.303–1.688)	<0.001*	1.287 (1.122–1.477)	<0.001*
Unknown	1.673 (1.467–1.908)	<0.001*	1.550 (1.350–1.780)	<0.001*
Marital status				
Unmarried ^b	1 (reference)		1 (reference)	
Married	0.887 (0.815–0.965)	0.005*	0.986 (0.901–1.080)	0.767
Unknown	1.134 (0.957–1.345)	0.147	1.195 (0.995–1.435)	0.056
Insurance status				
Uninsured	1 (reference)		1 (reference)	
Insured	0.878 (0.724–1.063)	0.183	1.044 (0.857–1.271)	0.670
Unknown	0.870 (0.623–1.213)	0.411	1.027 (0.725–1.455)	0.882

Notes: ^aIncluding other histology of invasive breast cancer except IDC and ILC; ^bIncluding divorced, separated, single (never married), and widowed; + denotes positive; – denotes negative; *denotes a statistically significant P-value.

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma.

tribution and prognosis of patients with BCLM; however, most mainly evaluate the occurrence of liver metastases after the diagnosis of early-stage breast cancer, while few focus on the patients who present with liver metastases upon

initial diagnosis of breast cancer.^{29–36} Since the previous systemic therapies and disease-free intervals may modify the natural course of liver metastases in recurrent breast cancer,^{3,37} it is meaningful to evaluate the prognostic factors

and outcomes of patients with BCLM at initial diagnosis in a large population-based analysis.

In this retrospective study, we identified 3,276 cases of liver metastases upon initial diagnosis of breast cancer between 2010 and 2014, accounting for 1.5% of all patients with breast cancer and 27.3% of the metastatic subgroup. This result is slightly different from the previously published literature. Diamond et al reported that nearly half of metastatic breast cancer patients have metastasis to the liver during the disease course.²⁰ In addition, Hoe et al reported an incidence of 5.2% among 912 breast cancer patients treated between 1982 and 1987.¹⁹ However, these two papers studied the liver metastases of patients diagnosed with early-stage breast cancer and not with synchronous liver metastases upon initial diagnosis of breast cancer. In addition, these two studies were based on small sample size analyses. Furthermore, the incidence of liver metastases may have changed dramatically over time due to the practice of early screening for breast cancer and the improvement of disease awareness.

There were significant differences in the clinicopathological characteristics of patients with BCLM when stratified by molecular subtype (Table 1). Compared with other patients, the HER2+ subtype and triple-negative subtype breast cancer patients with liver metastases more presented with high pathological grade, young age at diagnosis, and extrahepatic metastatic disease ($P < 0.001$). Additionally, we found an obvious discrepancy in the incidence of liver metastases when stratified by breast cancer subtype. Specifically, the HR+/HER2+ subtype and HR-/HER2+ subtype had the highest incidence of liver metastases, while the HR+/HER2- subtype had the lowest. Additionally, patients with the HR+/HER2+ subtype, HR-/HER2+ subtype, and triple-negative breast cancer had significantly greater odds of presenting liver metastases at initial diagnosis than patients with the HR+/HER2- subtype among the entire cohort and within the metastatic subgroup. These observations are in accordance with the findings of other publications studying the metastatic behaviors of breast cancer subtypes.^{9,11,12,38-42} The HER2+ enriched subtype and triple-negative subtype are more aggressive and have a tendency for visceral metastases. Upregulation of the chemokine receptor CXCR4 and enrichment of the PIK3-AKT-mTOR pathway, both relative to HER2 activation, are involved in promoting the metastasis of tumor cells to liver.^{43,44} Besides, Kimbung et al found that downregulation of extracellular matrix genes was associated with BCLM by whole-genome transcriptional profiling and significant analysis of microarray analyses.⁴⁵ The activities of matrix

metalloproteinases MMP-2 and MMP-9 had increased specifically after radiotherapy treatment in patients with BCLM, which was associated with poorer disease outcome.⁴⁶ The Notch1 signal pathway had been found to act as metastatic suppressor in the liver microenvironment.⁴⁷

In addition to the breast cancer subtypes mentioned earlier, we found that age at diagnosis, sex, pathological grade, and number of extrahepatic metastatic sites were associated with the presence of liver metastases in the multivariate logistic regression model among both the entire population and the metastatic subgroup. Similarly, Polivka et al studied the risk factors of brain metastases in patients diagnosed with breast cancer which included young age, premenopausal status, high tumor grade, breast cancer subtype, and specific protein and genetic markers.⁴⁸ Interestingly, our current result indicated that patients with older age at diagnosis had a decreased risk of liver metastases, which was consistent with the findings of previous studies.^{15,17,49} The multistep process from primary breast cancer tissue to liver metastasis is complicated. Semenza has summarized that the process of blood vessel metastases of breast cancer includes intravasation, circulation, margination, extravasation, and colonization.⁵⁰ Both breast cancer cell itself and the liver microenvironment are involved in this process.⁵¹ In addition, it may be possible that the capacity of these factors to facilitate metastases is compromised by the pathophysiological changes associated with aging. Purushotham et al discussed that deterioration of the immune system and alteration of the extracellular matrix accompanied by aging may explain this striking phenomenon.⁴⁹ In addition, we found that female patients had an increased risk of liver metastases compared with that of male patients in both the entire population and metastatic subgroup. Previous studies have reported that there exists a discordance in clinicopathological features between male breast cancer and female breast cancer.^{52,53} The association between gender and biological behavior of liver metastases needs further research. Here, we evaluated the predictive factors associated with liver metastases upon initial diagnosis of breast cancer, which may provide some reference for clinicians to distinguish those patients with a relatively high risk of liver metastases during the clinical course.

The median OS of patients with BCLM was 20 months, while patients with metastases confined to the liver had a median OS of 29 months. Recent studies have reported a median survival ranging from 24 to 33 months among patients with BCLM,^{54,55} which is in accordance with our results. Remarkably, we observed that the median survival of patients with BCLM varied significantly when stratified

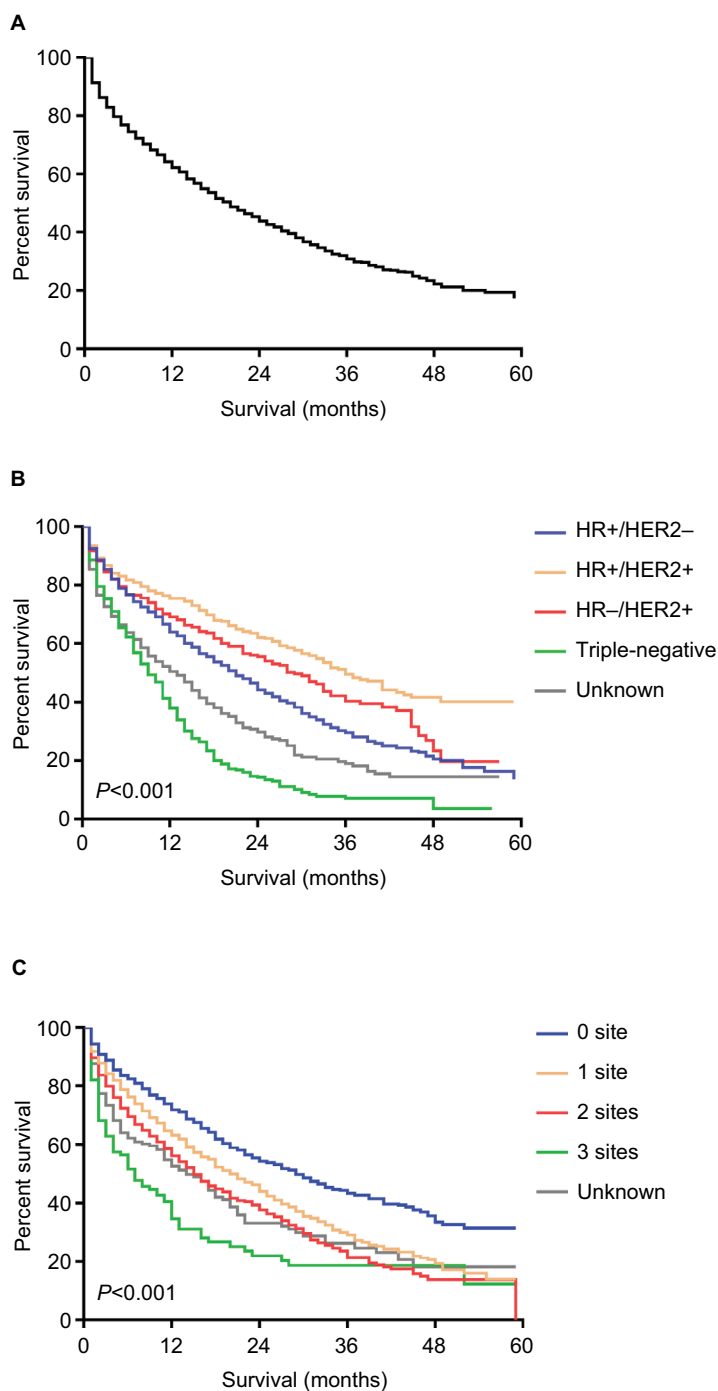


Figure 1 Kaplan–Meier curves for OS among patients with liver metastases upon initial diagnosis of breast cancer.

Notes: (A) OS. (B) OS stratified by the breast cancer subtype. (C) OS stratified by the extent of extrahepatic metastatic diseases.

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; + denotes positive; – denotes negative; OS: overall survival.

by tumor subtype. Specifically, HR+/HER2+ patients had the longest survival (median survival, 36.0 months), while triple-negative breast cancer patients had the shortest survival (median survival, 9.0 months). This result was slightly different from former publications. In a retrospective study, Duan et al had found that the median OS among patients with BCLM was 21–30, 32, and 41 months for the triple-

negative, HR-/HER2+, HR+/HER2-, and HR+/HER2+ subtypes, respectively.³⁴ In the multivariate Cox regression model, compared with HR+/HER2- breast cancer, the HR+/HER2+ subtype had a 33.4% reduction in hazards of overall mortality, while triple-negative patients experienced a 128% increase in overall mortality. The HR+/HER2+ subtype had a more favorable outcome than triple-negative subtype, which

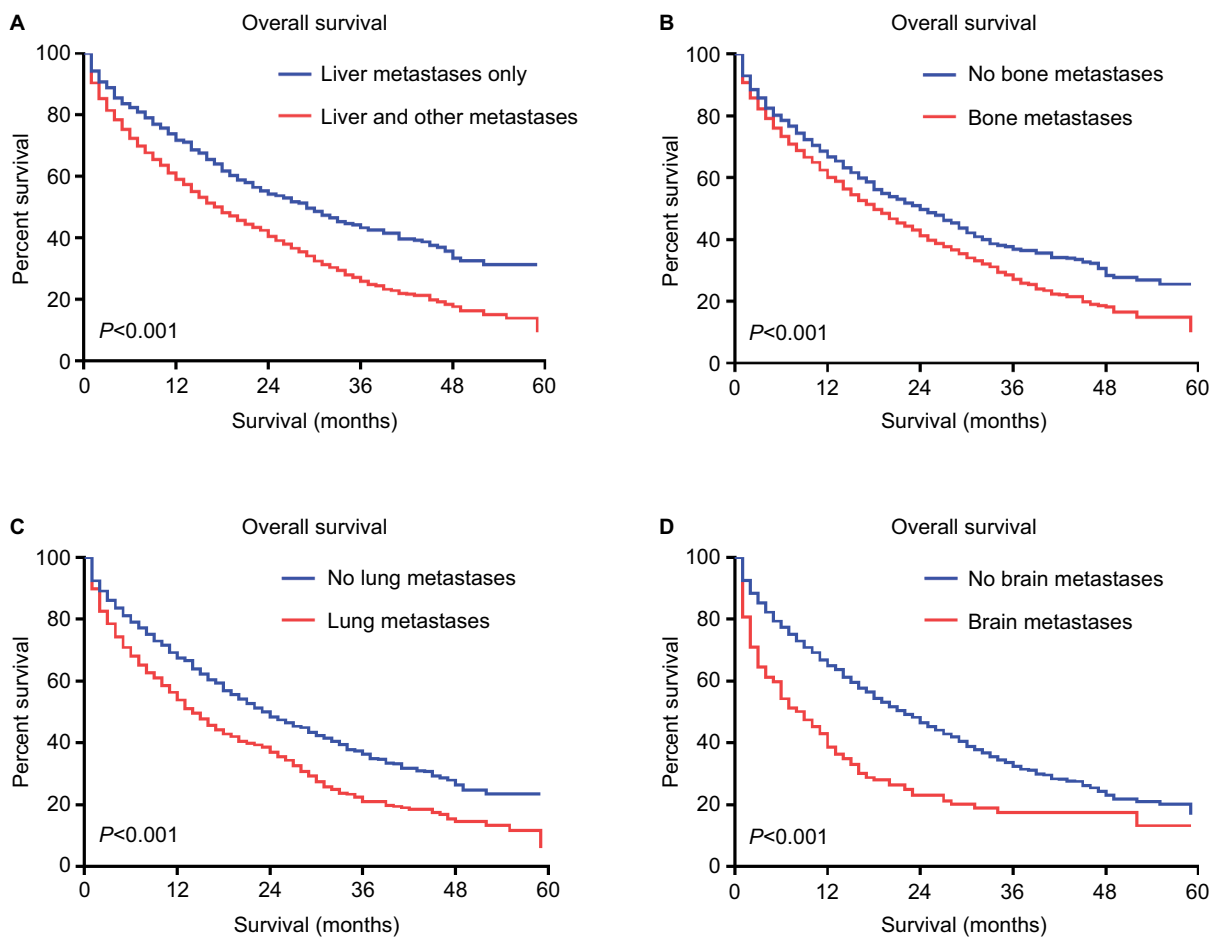


Figure 2 Kaplan–Meier curves for overall survival among patients with liver metastases according to individual metastases.

Notes: (A) Patients with only liver metastases vs those with liver and other metastases. (B) Patients with bone metastases vs those without bone metastases. (C) Patients with lung metastases vs those without lung metastases. (D) Patients with brain metastases vs those without brain metastases.

was consistent with some previous retrospective publications.^{35,42,56} We speculated that it may be mainly due to the improvement of HER2-targeted therapy, endocrine therapy, and the incorporation of chemotherapeutics, such as paclitaxel and anthracyclines.

The impact of the presence of extrahepatic metastases on the survival of patients with BCLM has been studied in previous studies.^{30–32,57} Wyld et al found that the presence of extrahepatic metastases was not significantly associated with the OS in patients with BCLM,³¹ while some papers reported that patients with liver and extrahepatic metastases had poorer survival than patients with metastases confined to the liver only.^{30,57} Atalay et al found that patients with liver metastases alone had longer survival than patients with liver plus other sites of metastases by a retrospective analysis of two prospective, randomized metastatic breast cancer trials.³² In the present study, we found that patients with only liver metastases had better survival than those simultaneously with extrahepatic metastases. Additionally, in the multivariate Cox

regression model, we observed that patients with more extrahepatic metastatic sites had a much higher hazard in overall mortality. Specifically, we identified that patients presenting with extrahepatic metastatic sites such as the lung, bone, and brain independently had worse survival than those without such metastatic sites by the survival comparison. Moreover, the influence of liver metastases on the OS of patients with extrahepatic metastases was evaluated. We found that among those patients with lung or bone metastases, the presence of liver metastases led to worse survival. However, the comparison did not reach significance in patients with brain metastases. We speculated that this result was due to the poor prognosis of breast cancer brain metastases itself with a median survival of 10 months.⁵⁸

Some limitations in our study should be acknowledged. First, the SEER database provides information about only four metastatic sites, namely, the lung, bone, brain, and liver. The presence of metastases in other sites, such as pleura and adrenal glands, is unknown, which may cause some bias in

Table 4 Median OS of breast cancer patients stratified by extent of extrahepatic metastatic disease

Breast cancer subtype	Type of extrahepatic metastasis	OS, median (IQR), months		P-value
		Extrahepatic metastatic disease only	Liver and extrahepatic metastatic disease	
HR+/HER2-	Bone	40.0 (21.0–NR)	23.0 (9.0–39.0)	<0.001*
	Lung	44.0 (14.0–57.0)	24.0 (7.0–33.0)	<0.001*
	Brain	12.0 (4.0–36.0)	6.0 (1.0–18.0)	0.125
	2 of 3	29.0 (12.0–55.0)	15.0 (6.0–34.0)	<0.001*
	All 3	17.0 (6.0–37.0)	13.0 (2.0–52.0)	0.791
HR+/HER2+	Bone	49.0 (27.0–NR)	35.0 (16.0–NR)	0.001*
	Lung	55.0 (22.0–NR)	26.0 (4.0–NR)	0.004*
	Brain	30.0 (13.0–NR)	NR	0.267
	2 of 3	42.0 (21.0–NR)	24.0 (6.0–NR)	<0.001*
	All 3	17.0 (5.0–NR)	8.0 (2.0–NR)	0.580
HR-/HER2+	Bone	NR (22.0–NR)	30.0 (11.0–45.0)	0.001*
	Lung	24.0 (11.0–NR)	25.0 (8.0–48.0)	0.605
	Brain	14.0 (8.0–38.0)	6.0 (4.0–6.0)	0.005*
	2 of 3	17.0 (6.0–NR)	24.0 (4.0–36.0)	0.613
	All 3	5.0 (3.0–9.0)	6.0 (3.0–16.0)	0.815
Triple-negative	Bone	14.0 (6.0–34.0)	7.0 (4.0–14.0)	<0.001*
	Lung	14.0 (6.0–26.0)	11.0 (5.0–18.0)	0.023*
	Brain	8.0 (3.0–19.0)	14.0 (3.0–22.0)	0.934
	2 of 3	9.0 (4.0–19.0)	7.0 (2.0–11.0)	0.064
	All 3	5.0 (3.0–18.0)	6.0 (1.0–12.0)	0.855
Unknown	Bone	24.0 (9.0–NR)	15.0 (5.0–29.0)	0.001*
	Lung	19.0 (4.0–50.0)	16.0 (4.0–26.0)	0.247
	Brain	10.0 (5.0–20.0)	1.0 (1.0–1.0)	<0.001*
	2 of 3	14.0 (3.0–39.0)	12.0 (2.0–28.0)	0.133
	All 3	13.0 (1.0–44.0)	2.0 (1.0–2.0)	0.059
All subtypes	Bone	38.0 (18.0–NR)	22.0 (8.0–43.0)	<0.001*
	Lung	25.0 (11.0–NR)	15.0 (5.0–31.0)	<0.001*
	Brain	13.0 (4.0–34.0)	6.0 (3.0–22.0)	0.261
	2 of 3	24.0 (9.0–NR)	15.0 (5.0–34.0)	<0.001*
	All 3	9.0 (4.0–34.0)	7.0 (2.0–22.0)	0.117

Notes: + denotes positive; – denotes negative; *denotes a statistically significant P-value.

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IQR, interquartile range; NR, not reached; OS, overall survival.

the prognostic assessment of the extrahepatic metastases subgroup. Furthermore, information on the extension and lesion of liver metastases is not available, which has been identified as an important prognostic factor among patients with BCLM.³⁴ Moreover, the database does not offer information about recurrence and later metastatic sites of disease. Therefore, patients who developed liver metastases would not be captured in the analysis. In addition, we do not have treatment information, such as information about whether patients received endocrine therapy, HER2-targeted therapy, or chemotherapy. Additionally, information about the local treatment of liver metastases was not available, which may contribute to some disparities in the survival analyses. Local treatment such as surgical liver resection or radiofrequency ablation has been studied, though the

current guidelines for patients with BCLM include mainly systemic palliative therapy.²⁰ In addition, the classification of breast cancer subtypes in the SEER database is mainly based on receptor status acquired by medical records from primary breast cancer. Recent studies have reported that some discordance exists in receptor status between primary and metastatic lesions, which may influence the statistical analysis of incidence and disease outcome of patients when stratified by breast cancer subtype.⁵⁹

Conclusion and expert recommendations

Studies have indicated that liver metastases from primary tumor is a complex process.^{26,50,51} Not only factors associated with breast cancer cells (inflammatory factors, chemokine

Table 5 Cox regression of OS and BCSS among patients with liver metastasis

Variable	OS						BCSS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	
Age at diagnose, years												
18-40	I (reference)		I (reference)		I (reference)		I (reference)		I (reference)		I (reference)	
41-60	1.523 (1.251-1.855)	<0.001*	1.445 (1.185-1.762)	<0.001*	1.548 (1.265-1.895)	<0.001*	1.464 (1.194-1.794)	<0.001*	1.464 (1.194-1.794)	<0.001*	1.464 (1.194-1.794)	<0.001*
61-80	2.327 (1.907-2.839)	<0.001*	2.113 (1.726-2.586)	<0.001*	2.285 (1.862-2.803)	<0.001*	2.059 (1.673-2.535)	<0.001*	2.059 (1.673-2.535)	<0.001*	2.059 (1.673-2.535)	<0.001*
>80	4.406 (3.453-5.621)	<0.001*	4.180 (3.248-5.379)	<0.001*	4.150 (3.221-5.347)	<0.001*	3.891 (2.994-5.058)	<0.001*	3.891 (2.994-5.058)	<0.001*	3.891 (2.994-5.058)	<0.001*
Sex												
Male	I (reference)		I (reference)		I (reference)		I (reference)		I (reference)		I (reference)	
Female	1.037 (0.517-2.077)	0.919	1.193 (0.589-2.417)	0.623	0.978 (0.488-1.959)	0.949	1.117 (0.552-2.264)	0.758	1.117 (0.552-2.264)	0.758	1.117 (0.552-2.264)	0.758
Race												
White	I (reference)		I (reference)		I (reference)		I (reference)		I (reference)		I (reference)	
Black	1.104 (0.970-1.256)	0.134	1.108 (0.970-1.267)	0.132	1.080 (0.945-1.235)	0.257	1.077 (0.938-1.236)	0.293	1.077 (0.938-1.236)	0.293	1.077 (0.938-1.236)	0.293
Asian/Pacific Islander	0.985 (0.805-1.207)	0.887	1.074 (0.876-1.317)	0.491	0.905 (0.729-1.123)	0.363	0.979 (0.788-1.217)	0.850	0.979 (0.788-1.217)	0.850	0.979 (0.788-1.217)	0.850
American India/Alaska	0.985 (0.528-1.836)	0.962	1.104 (0.590-2.068)	0.757	1.046 (0.561-1.950)	0.887	1.157 (0.617-2.167)	0.650	1.157 (0.617-2.167)	0.650	1.157 (0.617-2.167)	0.650
Unknown	0.537 (0.173-1.669)	0.283	0.577 (0.184-1.814)	0.347	0.565 (0.182-1.754)	0.323	0.596 (0.189-1.874)	0.376	0.596 (0.189-1.874)	0.376	0.596 (0.189-1.874)	0.376
Histology												
IDC	I (reference)		I (reference)		I (reference)		I (reference)		I (reference)		I (reference)	
ILC	1.138 (0.929-1.394)	0.212	1.089 (0.878-1.351)	0.438	1.147 (0.932-1.412)	0.196	1.106 (0.887-1.380)	0.371	1.106 (0.887-1.380)	0.371	1.106 (0.887-1.380)	0.371
Others ^a	1.344 (1.191-1.518)	<0.001*	1.163 (1.014-1.333)	0.031*	1.328 (1.172-1.506)	<0.001*	1.136 (0.986-1.308)	0.077	1.136 (0.986-1.308)	0.077	1.136 (0.986-1.308)	0.077
Pathological grade												
I	I (reference)		I (reference)		I (reference)		I (reference)		I (reference)		I (reference)	
II	1.083 (0.809-1.449)	0.592	1.186 (0.879-1.601)	0.265	1.094 (0.808-1.482)	0.562	1.191 (0.872-1.627)	0.272	1.191 (0.872-1.627)	0.272	1.191 (0.872-1.627)	0.272
III/IV	1.302 (0.981-1.730)	0.068	1.517 (1.125-2.046)	0.006*	1.333 (0.992-1.791)	0.056	1.533 (1.124-2.093)	0.007*	1.533 (1.124-2.093)	0.007*	1.533 (1.124-2.093)	0.007*
Unknown	1.468 (1.093-1.971)	0.011*	1.294 (0.949-1.763)	0.103*	1.508 (1.110-2.049)	0.009*	1.318 (0.955-1.817)	0.093	1.318 (0.955-1.817)	0.093	1.318 (0.955-1.817)	0.093
Surgery												
No surgery	I (reference)		I (reference)		I (reference)		I (reference)		I (reference)		I (reference)	
BCS	0.678 (0.557-0.825)	<0.001*	0.750 (0.613-0.918)	0.005*	0.685 (0.560-0.838)	<0.001*	0.759 (0.617-0.934)	0.009*	0.759 (0.617-0.934)	0.009*	0.759 (0.617-0.934)	0.009*
Mastectomy	0.601 (0.521-0.692)	<0.001*	0.648 (0.558-0.752)	<0.001*	0.589 (0.509-0.683)	<0.001*	0.637 (0.546-0.744)	<0.001*	0.637 (0.546-0.744)	<0.001*	0.637 (0.546-0.744)	<0.001*
Unknown	0.291 (0.121-0.700)	0.006*	0.350 (0.144-0.852)	0.021*	0.308 (0.128-0.741)	0.009*	0.357 (0.147-0.869)	0.023*	0.357 (0.147-0.869)	0.023*	0.357 (0.147-0.869)	0.023*
Number of extrahepatic metastatic sites to lung, bone, and brain												
0	I (reference)		I (reference)		I (reference)		I (reference)		I (reference)		I (reference)	
1	1.424 (1.248-1.625)	<0.001*	1.250 (1.092-1.431)	0.001*	1.465 (1.278-1.680)	<0.001*	1.295 (1.126-1.489)	<0.001*	1.295 (1.126-1.489)	<0.001*	1.295 (1.126-1.489)	<0.001*
2	1.734 (1.496-2.009)	<0.001*	1.605 (1.379-1.868)	<0.001*	1.753 (1.504-2.043)	<0.001*	1.633 (1.394-1.911)	<0.001*	1.633 (1.394-1.911)	<0.001*	1.633 (1.394-1.911)	<0.001*
All 3	2.622 (2.062-3.335)	<0.001*	2.254 (1.762-2.882)	<0.001*	2.747 (2.148-3.513)	<0.001*	2.361 (1.836-3.037)	<0.001*	2.361 (1.836-3.037)	<0.001*	2.361 (1.836-3.037)	<0.001*
Unknown	1.816 (1.469-2.245)	<0.001*	1.580 (1.272-1.963)	<0.001*	1.939 (1.563-2.405)	<0.001*	1.701 (1.364-2.120)	<0.001*	1.701 (1.364-2.120)	<0.001*	1.701 (1.364-2.120)	<0.001*
Breast cancer subtype												

(Continued)

Table 5 (Continued)

Variable	OS			BCSS		
	Univariate analysis		Multivariate analysis	Univariate analysis		Multivariate analysis
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)
HR ⁺ /HER2 ⁻	I (reference)		I (reference)	I (reference)		I (reference)
HR ⁺ /HER2 ⁺	0.609 (0.523–0.708)	<0.001*	0.666 (0.571–0.778)	0.626 (0.536–0.731)	<0.001*	0.682 (0.582–0.800)
HR ⁻ /HER2 ⁺	0.808 (0.686–0.953)	0.011*	0.909 (0.767–1.077)	0.824 (0.696–0.977)	0.026*	0.924 (0.776–1.100)
Triple-negative	2.067 (1.798–2.376)	<0.001*	2.283 (1.968–2.649)	2.123 (1.839–2.451)	<0.001*	2.346 (2.013–2.735)
Unknown	1.488 (1.268–1.745)	<0.001*	1.336 (1.130–1.580)	1.548 (1.315–1.823)	<0.001*	1.395 (1.175–1.656)
Marital status						
Unmarried ^b	I (reference)		I (reference)	I (reference)		I (reference)
Married	0.769 (0.693–0.853)	<0.001*	0.863 (0.775–0.962)	0.778 (0.699–0.866)	<0.001*	0.865 (0.773–0.967)
Unknown	0.918 (0.743–1.136)	0.433	0.891 (0.717–1.107)	0.929 (0.747–1.156)	0.511	0.895 (0.715–1.119)
Insurance status						
Uninsured	I (reference)		I (reference)	I (reference)		I (reference)
Insured	0.734 (0.578–0.932)	0.011*	0.741 (0.580–0.947)	0.745 (0.582–0.954)	0.020*	0.765 (0.594–0.986)
Unknown	0.807 (0.534–1.220)	0.309	0.744 (0.487–1.135)	0.846 (0.554–1.290)	0.437	0.787 (0.511–1.213)

Notes: ^aIncluding other histology of invasive breast cancer except IDC and ILC; ^bIncluding divorced, separated, single (never married), and widowed; + denotes positive; – denotes negative; *denotes a statistically significant P-value. Abbreviations: BCS, breast conserving surgery; BCSS, breast cancer-specific survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; OS, overall survival.

and chemokine receptors, cell adhesion molecules, claudins, and breast cancer subtypes) but also factors associated with liver microenvironment (hypoxia-inducible factor-regulated genes, vasculature, and sinusoidal capillaries) are involved in this process.⁵¹ The advancement of multi-omics approaches of clinical samples from patients with BCLM individually would further unveil the mystery of liver metastases.^{27,28} Nowadays, distant metastases of breast cancer are related to poor disease outcome,² and it is meaningful to study the risk factors of breast cancer patients predisposed to liver metastases for early intervention and prognostic factors of patients with BCLM for personalized therapy, which was our current study's aim. To our knowledge, this is the first large population-based study of patients with liver metastases at initial diagnosis of breast cancer. Our study has strong external validity and provides essential information about the clinicopathological characteristics, incidence, and prognosis of patients with BCLM. The results can inform early screening, risk evaluation, and prognosis guidance for patients with BCLM. However, whether these changes in clinical course could have an impact on disease outcome warrants further prospective research.

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Author contributions

Conception and design: HYZ, YG, FGY, HL, and XH. Development of methodology: HYZ, YG, and FGY. Acquisition of data: HYZ and FGY. Analysis and interpretation of data: HYZ, YG, FGY, HL, and HX. Writing, review, and/or revision of manuscript: HYZ, HL, and HX. Study supervision: HL and XH. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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